

TABLE A3.—Outline of methods used in retrospective studies of smoking in relation to lung cancer (cont.)

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Randig, 1954, Germany (218).	M-F	448 lung cancer patients in a number of West Berlin hospitals.	512 patients with other diagnoses, matched for age.	Controls were interviewed at about the same time as the cases, each case-control pair by the same physician.
Wynder et al., 1956, U.S.A. (311).	F	105 patients with lung cancer in several New York City hospitals.	1,304 patients at Memorial Center with tumors of sites other than respiratory or upper alimentary.	Cases: Personal interview or questionnaire mailed to close relatives or friends. Controls: Personal interview.
Segi et al., 1957, Japan (250).	M-F	207 patients with lung cancer in 33 hospitals in all parts of the country.	5,636 patients free of cancer in 420 local health centers, selected to approximate the sex and age distributions of cases.	Cases and controls by personal interview using long questionnaire on occupational and medical history and living habits.
Mills and Porter, 1957, U.S.A. (187).	M-F	578 residents of defined areas dying of respiratory cancer.	3,310 population sample approximately proportional to cases as regards areas of residence, and 10 years or more in the area.	Cases: From death certificates, hospital records, and close relatives or friends. Controls: Personal home visits or telephone calls, usually interviewing housewife.
Stocks, 1957, England (268).	M-F	2,356 patients suffering from or dying with lung cancer within certain areas.	9,362 unselected patients of the same area admitted for conditions other than cancer.	Cases: Histories taken at the hospital from relatives by health visitors. Controls: Personal interview in hospital.
Schwartz and Denois, 1957, France (247).	M	602 patients with bronchopulmonary cancer in hospitals.	1,204 patients (3 groups) in same hospitals with other cancer, with nonmalignant illness, and accident cases, matched by age group.	Personal interviews in the hospital; cases and controls at about the same time by the same interviewer.

TABLE A3.—Outline of methods used in retrospective studies of smoking in relation to lung cancer (cont.)

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Haenszel and Shimkin, 1958, U.S.A. (113).	F	158 lung cancer patients available for interview in 29 hospitals.	339 patients in same hospital and service at same time, next older and next younger than each case.	Personal interviews by resident, medical social worker, or clinic secretary.
Lombard and Snegireff, 1959, U.S.A. (176).	M	500 men dying of lung cancer, microscopically confirmed.	4,238 controls in 7 groups including volunteers, hospital and clinic patients, random population sample, and house-to-house survey samples.	Personal interviews by trained workers.
Pernu, 1960, Finland (211).	M-F	1,606 respiratory cancer patients in 4 hospitals and from cancer registry.	1,773 cancer-free persons recruited by Parish Sisters of 2 institutes in all parts of the country.	Cases: From case histories or mailed questionnaires. Controls: Questionnaires distributed by Parish Sisters.
Haenszel et al., 1962, U.S.A. (112).	M	2,191 sample of 10 percent of white male lung cancer deaths in the U.S.A. in 1958.	31,516 random sample from Current Population Survey.	Cases: By mail from certifying physicians and family informants. Controls: Personal interview by census enumerators.
Lancaster, 1962, Australia (158).	M	238 hospital patients with lung cancer.	476 in 2 groups, 1 with other cancer, 1 with some other disease, matched by sex and age.	Personal interviews of both cases and controls in hospitals.
Haenszel and Taeuber, 1964, U.S.A. (115).	F	749 sample of 10 percent of white female lung cancer deaths in the U.S.A. in 1958 and 1959.	34,339 random sample from Current Population Survey used to estimate population base.	Cases: By mail from certifying physicians and family informants. Controls: Personal interview by census enumerators.

TABLE A3.—Outline of methods used in retrospective studies of smoking in relation to lung cancer (cont.)

Author, year, country, reference	Sex of cases	Number of persons and method of selection		Collection of data
		Cases	Controls	
Wicken, 1966, Northern Ireland (308).	M-F	954 patients with primary lung cancer.	954 age and sex-matched controls from same locale and deceased from nonrespiratory diseases.	Interviews with relatives.
Gelfand et al., 1968, Rhodesia (22).	M	32 patients with bronchogenic cancer.	32 age and sex-matched patients	Hospitalization interviews.
Hitosugi, 1968, Japan (126).	M-F	185 patients with lung cancer	491 persons sex-matched from similar air-pollution regions.	Cases: Hospital interviews. Controls: Interviews by trained public health nurses.
Bradshaw and Schorland, 1969, South Africa (Natal) (41).	M	45 Zulu patients with lung cancer.	341 Zulu patients without lung cancer.	Interviewed by trained African social worker.
Ormos et al., 1969, Hungary (204).	M-F	118 patients with lung cancer.	3,089 control persons without data on health history.	Cases: Data derived from case histories and interviews with relatives. Controls: Interviews with a random sample of train passengers.
Wynder, et al., 1970 U.S.A. (324).	M-F	240 patients with Kreyberg Type I lung cancer.	480 age and sex-matched patients	Hospitalization interview.

TABLE A4.—Group characteristics in retrospective studies on lung cancer and tobacco use

SM = Smokers. NS = Nonsmokers.

Author, year, reference	Males						Females						Relative risk ratio SM:NS ²	Comments	
	Cases			Controls			Cases			Controls					
	Number	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹			
Müller, 1939 (196).	86	3.5	65.1	86	16.3	36.0	5.4	(*)	(*)	(*)	(*)	(*)	(*)	...	
Schairer and Schöniger, 1943 (242).	93	3.2	31.2	270	15.9	9.3	5.7	(*)	(*)	(*)	(*)	(*)	(*)	...	16 female cases not analyzed.
Potter and Tully, 1945 (212).	43	7.0	30.2	2,804	26.0	23.0	4.1	(*)	(*)	(*)	(*)	(*)	(*)	...	
Wassink, 1948 (304).	134	4.8	54.8	100	19.2	19.2	4.7	(*)	(*)	(*)	(*)	(*)	(*)	...	Percentages estimated from chart.
Schrek et al., 1950 (246).	82	14.6	18.3	522	23.9	9.2	1.8	(*)	(*)	(*)	(*)	(*)	(*)	...	
Mills and Porter, 1950 (186).	444	7.2	...	430	30.5	...	5.7	(*)	(*)	(*)	(*)	(*)	(*)	...	
Levin et al., 1950 (171).	236	15.3	...	481	21.7	...	1.5	(*)	(*)	(*)	(*)	(*)	(*)	...	Quantity smoked not considered.
Wynder and Graham, 1950 (316).	605	1.3	51.2	780	14.6	19.1	13.0	40	57.5	25.0	552	79.6	1.2	2.9	

TABLE A4.—Group characteristics in retrospective studies on lung cancer and tobacco use (cont.)

SM = Smokers. NS = Nonsmokers.

Author, year, reference	Males							Females							Comments	
	Cases			Controls				Relative risk ratio SM:NS ²	Cases			Controls				Relative risk ratio SM:NS ²
	Num- ber	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Number		Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹			
Randig, 1954 (218).	415	1.2	34.2	381	5.8	17.9	35.1	33	51.5	3.0	131	70.3	0	2.2		
Wynder et al., 1956 (311).	(*)	(*)	(*)	(*)	(*)	(*)	...	105	56.2	16.2	1,304	66.0	3.4	1.4		
Segi et al., 1957 (250).	166	2,124	Quantities smoked stated as averages only. Differences are statistically significant.	
Mills and Porter, 1957 (187).	484	8.4	26.0	1,588	27.6	5.3	4.2	94	83.0	4.3	1,722	73.3	0.5	0.6	Percent "heavy" smokers under- stated. Only 50% survey response among female cases.	
Stocks, 1957 (263).	2,101	1.9	28.2	5,960	8.7	22.3	4.9	255	57.6	17.2	3,402	68.6	10.7	1.6		
Schwartz and Denoix, 1957 (247).	602	1.0	58.2	1,204	9.5	36.2	10.4	(*)	(*)	(*)	(*)	(*)	(*)	...		
Haenszel and Shimkin, 1958 (113).	(*)	(*)	(*)	(*)	(*)	(*)	...	158	51.9	14.6	339	69.6	8.2	2.5		

TABLE A4.—Group characteristics in retrospective studies on lung cancer and tobacco use (cont.)

SM = Smokers. NS = Nonsmokers.

Author, year, reference	Males						Females						Relative risk ratio SM:NS ²	Comments	
	Cases			Controls			Cases			Controls					
	Num- ber	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹			
Lombard and Snegireff, 1959 (176).	500	1.6	...	4,238	11.0	...	7.9	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	...	Authors' calculations for heavy smoking based on lifetime number of packs of cigarettes.
Pernu, 1960 (211).	1,477	6.6	34.5	713	37.2	20.8	8.4	129	85.3	26.4	1,060	91.6	0.7	1.9	Quantities given only in grams per day.
Haenszel et al., 1962 (112).	2,191	3.4	41.9	(⁴)	16.2	12.0	5.2	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	...	Population sample of 31,516 used as base. Not a case- control study.
Lancaster, 1962 (158).	238	2.5	86.1	476	20.1	71.2	9.8	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	...	
Haenszel and Taeuber, 1964 (115).	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	...	749	60.9	11.5	(⁴)	67.3	2.5	1.3	Population sample of 34,339 used as base. Not a case-control study.

TABLE A4.—Group characteristics in retrospective studies on lung cancer and tobacco use (cont.)

SM = Smokers. NS = Nonsmokers.

Author, year, reference	Males						Females						Relative risk ratio SM:NS ²	Comments	
	Cases			Controls			Cases			Controls					
	Num- ber	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹	Number	Percent non- smokers	Percent heavy smokers ¹			
Wicken, 1966 (308).	803	4.0	40.0	803	14.0	22.0	3.9	151	58.0	29.0	151	80.0	17.0	2.9	Heavy smokers— greater than 23 a day.
Gelfand et al., 1968 (98).	32	6.3	...	32	63.0	...	² 25.3	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	...	
Hitosugi, 1968 (125).	124	5.6	67.8	1,839	13.2	55.0	2.6	61	54.1	6.6	2,352	80.5	2.9	2.3	Air pollution found to have no effect on lung cancer rates of non- smokers. Heavy smokers—great- er than 15 a day.
Bradshaw and Schonland, 1969 (41).	45	0.0	...	341	31.7	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	(⁴)	...	
Ormos et al., 1969 (204).	94	7.5	58.5	1,811	42.9	38.9	9.3	24	95.8	0.0	1,278	81.7	9.7	0.2	Heavy smokers— greater than 15 a day.
Wynder et al., 1970 (334).	210	1.4	67.5	420	21.0	40.9	² 20.8	30	16.7	44.0	132	57.6	23.3	6.78	Heavy smokers— greater than 20 a day.

¹ For this table, heavy smokers are defined as those smoking 20 or more cigarettes per day, unless otherwise stated.² Computed according to method of Cornfield, J. (61).³ Based upon fewer than 5 case nonsmokers.⁴ Does not apply.

TABLE A7.—*Grouping of pulmonary carcinomas*

Group I:

- A. Epidermoid carcinoma.
- B. Small cell anaplastic carcinoma ("oat-cell" carcinoma).

Group II:

- A. Adenocarcinoma.
- B. Bronchiolo-alveolar cell carcinoma.
- C. Carcinoid tumor.
- D. Mucous gland tumor.

Extra (not included in I and II):

- A. Large cell undifferentiated carcinoma.
- B. Combined epidermoid and adenocarcinoma.

Unsuitable for diagnosis.

SOURCE: Kreyberg, L. (153).

TABLE A12.—Autopsy studies concerning the presence of radioactivity in the lungs of smokers
 NS = Nonsmokers. SM = Smokers.

Author, year, country, reference	Number of cases	Results				Comments	
Little et al., 1964, U.S.A. (173).		<i>Po²¹⁰ levels in various tissues (pc/g tissue)</i>				Vertebral bodies, renal cortex, spleen, and urinary bladder showed no differences.	
		<i>Peribronchia! lymph nodes</i>	<i>Lung (average)</i>		<i>Bronchial epithelium negligible</i>		
	NS	5	0.011	0.001-2	0.028-1.25		
	SM	12	0.011	0.008			
Hill, 1965, U.S.A. (123).		<i>Mean Po²¹⁰ levels in various tissues (pc/kg tissue)</i>					The authors found no excessive concentrations at bronchial bifurcations.
		<i>Bronchial tree</i>	<i>Alveolae</i>	<i>Total lung</i>	<i>Liver</i>	<i>Kidney</i>	
	NS	6	3.1	3.4	3.2	14.8	
	SM	4	7.3	9.9	8.6	20.0	20.5
Little et al., 1965, U.S.A. (174).		<i>Po²¹⁰ levels in various epithelial tissue regions of lung (pc/g) †</i>				The authors noted considerable interpersonal variation but did find a trend relationship between increased daily consumption and increased <i>Po²¹⁰</i> levels in lung parenchyma. No such relationship was noted for age of individual at death or for total pack-years.	
			Site:				
	NS	8	Mainstem bronchus	<0.2- 1.7			
			Lobar bronchus	<0.2- 1.0			
	SM	25	Basal segmental bronchus	<0.2- 2.6			
			Upper segmental bifurcation	<0.5- 7.8			
		Lower segmental bifurcation	<0.5-13.9				
			†Smokers only.				

TABLE A12.—Autopsy studies concerning the presence of radioactivity in the lungs of smokers (cont.)

NS = Nonsmokers. SM = Smokers.

Author, year, country, reference	Number of cases	Results			Comments
		<i>Mean Po²¹⁰ levels in various tissues (pc/g wet tissue)</i>			
Ferri and Baratta, 1966, U.S.A. (95).	NS10 SM14	<i>Lung</i>	<i>Liver</i>	<i>Kidney</i>	
		0.031	0.103	0.080	
		0.065	0.125	0.070	
		<i>Mean Po²¹⁰ levels in various tissues (pc/g)</i>			
Rajewsky and Stahlhofen, 1966, Germany (217).	NS † SM12	<i>Lung parenchyma</i>	<i>Bronchial tree</i>	<i>Bronchial bifurcation</i>	† Data not given. Smokers were considered those using more than 1 pack a day. The authors noted that their figures were con- siderably smaller than those of Little et al. (173, 174) and also disagreed with their data on bifurcation.
		0.0025	0.0020	0.0012	
		0.0078	0.0077	0.0047	
		<i>Mean Po²¹⁰ levels in various epithelial tissues (pc/g wet tissue)</i>			
Little and Radford, 1967, U.S.A. (172).	SM25 Pipe 2 Ex-cigarette 1 Never 8	Bronchial wall and submucosa			0.004
		Bronchial epithelium:			
		Trachea			0.120
		Lobar bronchi			0.190
		Segmental bifurcation			4.500

TABLE A13.—Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results	Comments	
Wynder et al., 1953, U.S.A. (317).	CAF ₁ mice	A. Painting shaved skin.	<i>Percent animals with:</i>		† Number in parenthesis represents total in that experimental group. Skin-painting experiments prior to 1953 are fully detailed in tabular form in this article.
		B. 3/week for 2 years.	<i>Papillomas†</i>		
		C. Whole cigarette smoke condensate in acetone.	<i>Cancer†</i>		
		Croton oil once/week.	59.0 (81)	44.0 (81)	
			42.0 (31)	9.7 (31)	
		(30)	(30)		
		Acetone and croton oil	(14)	(14)	
Passey et al., 1955, England (209).	5 different mouse strains (101).	A. Painting unshaven skin. B. 2/week for 9 months. C. Whole "tar" or neutral fraction.	No malignant tumor noted in either group. Papilloma noted on one animal (in whole "tar" group) which later regressed.		
Orr et al., 1955, England (205).	Mice of 2 strains.	A. Painting skin.	<i>Number animals with:</i>		
		B. 1 or 2/week for 18 months.	<i>Papillomas</i>		
		C. 20 percent cigarette "tar" in acetone. 0.3 percent benzpyrene.	Benzpyrene 1/week followed by "tar" 2/week.	4/30 at 18 months (separate group received only benzpyrene and showed no tumors).	
		"Tar" alone	0/50 at 18 months.		

TABLE A13.—*Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results			Comments	
			Strain	Papillomas	Carcinomas		
Wynder et al., 1955, U.S.A. (318).	Mice of 4 separate strains.	A. Painting shaved skin.	<i>Strain</i>	<i>Papillomas</i>	<i>Carcinomas</i>	No tumors noted with acetone alone. Stresses differences in susceptibility of strain.	
		B. 3/week for 80 days.	C57BL	10/89	2/89		
		C. Whole condensate in acetone.	Swiss	22/86	12/86		
Hamer and Woodhouse, 1956, U.S.A. (116).	Outbred albino strain mice.	A. Painting unshaved skin.	<i>Treatment:</i>		<i>Papillomas</i>		
		B. Varied for 18 months.	"Tar" 2/week	1/50			
		C. Whole "tar"/acetone, benzpyrene [B(a)P], croton oil.	"Tar" and croton oil 1/week.	2/30			
			B (a) P 3 times then "tar" 2/week	4/30			
		B (a) P 3 times	0/30				
Sugiura, 1956, U.S.A. (266).	Rockland Swiss albino mice (60).	A. Painting unshaved skin.	<i>Papillomas</i>	<i>Carcinomas</i>	(only 44/60 lived from 365-696 days).		
		B. 3/week for 2 years.	16/44	12/44			
		C. Whole "tar".					
Graham et al., 1957, U.S.A. (101).	Albino New Zealand rabbits.	A. Painting shaved skin.	<i>Treatment:</i>		<i>Papillomas</i>	<i>Carcinomas</i>	The authors review previous experiments with rabbits in tabular form.
		B. 3/week for 6 years.	Condensate	41/41	5/41		
		C. Whole condensate.	Condensate and croton oil 1/week.	10/10	2/10		
			Croton oil and acetone 1/week.	0/3	0/3		
		Acetone 1/week	0/7	0/7			
Guerin and Cuzin, 1957, U.S.A. (109).	Mice (Pasteur strain.)	A. Painting neck skin.	<i>Original number</i>	<i>Survivors</i>	<i>Papillomas</i>	<i>Sarcomas</i>	† Control group.
		B. 2/week for >1 year.	†C. 112	51	0/51	0/51	‡ Experimental group.
		C. Whole condensate.	‡E. 672	220	10/220	5/220	

TABLE A13.—Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results			Comments	
Wynder et al., 1957, U.S.A. (323).	Swiss mice	A. Painting skin.					
		B. Varied for 12 months.	<i>Treatment:</i>	<i>Number</i>	<i>Percent papillomas</i>	<i>Percent carcinomas</i>	
			5/week	50	12.0	8.0	
		C. Whole condensate in acetone.	3/week	50	38.0	16.0	
			2/week	40	10.0	3.0	
		1/week	40	6.0	...		
Wynder and Wright, 1957, U.S.A. (328).	CAF ₁ or Swiss mice.	A. Painting shaved skin.					
		B. 3/week for lifespan.	<i>Treatment CAF₁:</i>	<i>Number</i>	<i>Percent papillomas</i>	<i>Percent carcinomas</i>	
		C. Whole "tar" or nicotine free "tar" derived from pipe and cigarette tobacco.	Whole "tar"	30	53.0	27.0	Swiss mice noted to be more susceptible. Majority of carcinogens noted to be in neutral fraction of condensate.
			Nicotine free "tar"	40	73.0	25.0	
			Cigarette "tar"	30	30.0	30.0	
			Pipe "tar"	30	60.0	20.0	
			<i>Treatment Swiss:</i>				
			Whole "tar"	30	53.0	10.0	
			Nicotine free "tar"	40	43.0	20.0	
			Cigarette "tar"	30	63.0	33.0	
	Pipe "tar"	30	63.0	50.0			
Gellhorn, 1958, U.S.A. (99).	Paris R III mice	A. Painting shaved skin.	<i>Treatment:</i>	<i>Papillomas</i>	<i>Carcinomas</i>		
		B. Varied for 1-2 years.	Benzpyrene (twice only)	20/529	5/529		
		C. "Tar" in acetone, benzpyrene, croton oil.	Croton oil (5/6 week)	4/26	0/26		
			"Tar" (5/6 week)	3/559	2/559		
			Acetone (5/6 week)	0/30	0/30		
		"Tar" and croton oil (5/6 week)	10/175	0/175			
Bock and Moore, 1959, U.S.A. (28).	Swiss female mice	A. Painting skin.			<i>Percent</i>		
		B. 5/week for lifespan.	<i>Group:</i>	<i>Number living at 6 months</i>	<i>Skin tumors at 64 weeks</i>		
		C. Whole condensate irradiation.	Painted	49	13.0		
			Painted and irradiated	65	44.0		
		Irradiated	36	...			

TABLE A13.—*Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results			Comments	
Druckrey, 1961, Germany (78).	Rats	A. Subcutaneous injection. B. 1/week for 60 weeks. C. Smoke condensate in tricapyrylin and alcohol.	<i>Group:</i>		<i>Sarcomas</i>	† Control group. ‡ Experimental group.	
			† C	1/75			
			‡ E	15/75			
Bock et al., 1962, U.S.A. (31).	ICR Swiss mice	A. Painting shaved skin. B. 10/week for 1 year. C. Cigarette "tar".	<i>Treatment:</i>		<i>Surviving at 18 weeks</i>	<i>Percent Skin cancer</i>	<i>Percent Skin neoplasia</i>
			Standard cigarette	24/30	25.0	54.0	
			Standard cigarette	21/30	5.0	57.0	
			Standard cigarette	18/30	33.0	44.0	
			Standard cigarette	13/30	23.0	62.0	
			Filter cigarette	30/30	7.0	27.0	
			Filter cigarette	30/30	3.0	23.0	
			Acetone only	66/66	
Control	65/65				
Roe, 1962, U.S.A. (225).	Albino mice	A. Painting shaved skin. B. 3/week for 84 weeks. C. Whole smoke "tar" with added B(a)P in acetone.	<i>Treatment:</i>		<i>Survivors</i>	<i>Percent skin tumors</i>	Author concluded that cigarette smoke contains cocarcinogens.
			"Tar" and 0.025 mg. B(a)P	26	12.0		
			"Tar" and 0.06 mg. B(a)P	15	27.0		
			"Tar" and 0.25 mg. B(a)P	15	13.0		
			"Tar" and 1.25 mg. B(a)P	14	64.0		
B(a)P 1.25 mg.	14	...					
Druckrey and Schildbach, 1963, Germany (82).	Rats	A. Subcutaneous injection. B. 1/week for 700 days. C. Benzpyrene in tricapyrylin.	<i>Treatment (BP mg./week):</i>		<i>Sarcomas</i>		
			30	25/30			
			10	14/40			
			3	8/50			
			— (solvent)	2/75			

TABLE A13.—Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)

Author, year, country, reference	Animal and strain	A. Method, B. Frequency and/or duration, C. Material	Results			Comments	
Homburger et al., 1968, U.S.A. (181).	CAF ₁ mice	A. Painting shaved skin. B. 2-3/week for 2 years. C. Various tobacco condensates in acetone.	<i>Condensate:</i>	<i>Complete autopsies</i>	<i>Percent Papillomas</i>	<i>Percent Carcinomas</i>	
				Pipe tobacco	77	35.0	15.0
				Cigar tobacco	84	27.5	15.0
				Cigarette tobacco	82	27.0	15.0
				Benzpyrene	54	10.0	20.0
				Acetone only	62
Bock et al., 1965, U.S.A. (29).	Swiss ICR mice	A. Painting clipped skin. B. 10/week for 11 weeks. C. Various smoke condensates in acetone.	Percent concentration of tar (type cigarette):	<i>Percent surviving 11 weeks</i>	<i>Percent cancer</i>	<i>Percent cancer and papilloma</i>	
				9.2 (standard)	96.0	30.0	67.0
				8.3 (standard)	93.0	27.0	67.0
				7.9 (English standard)	90.0	24.0	58.0
				8.7 (king)	100.0	28.0	69.0
				4.0 (filter)	98.0	9.0	36.0
				4.4 (filter)	100.0	10.0	41.0
				2.5 (filter)	97.0	4.0	16.0
				Acetone control	94.0
				Untreated control	100.0
				Van Duuren et al., 1966, U.S.A. (296).	Swiss ICR/ Ha mice	A. Painting shaved skin. B. Initiating agent once—Promoter 3/week for 12-14 months. C. DMBA†, tobacco extracts cigarette "tar".	<i>Initiator Promoter</i>
	<i>Papillomas</i>	<i>Carcinomas</i>					
DMBA ... Ether tobacco leaf extract	4/20	0/20					
O ... Ether tobacco leaf extract	0/20	0/20					
DMBA ... Chloroform tobacco leaf extract	1/20	0/20					
O ... Chloroform tobacco leaf extract	0/20	0/20					
DMBA ... Cigarette "tar"	11/20	4/20					
O ... Cigarette "tar"	0/20	0/20					
O ... Acetone	0/20	0/20					

TABLE A13.—*Experiments concerning the effects of the skin painting or subcutaneous injection of cigarette smoke condensate or its constituents upon animals (cont.)*

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration, C. Material	Results				Comments	
Munoz et al., 1968, U.S.A. and Colombia (197).	Swiss ICR/4a mice	A. Painting shaved skin.	<i>Dark tobacco "tar"</i>	<i>At risk</i>	<i>Tumors</i>	<i>Carcinomas</i>	The authors noted a shortened latent period for dark tobacco.	
		B. Varied.	4.0 percent	81	50	17		
		C. "Tar" from dark (Colombian) and light (U.S.A.) tobaccos.	8.0 percent	71	46	16		
			<i>Light tobacco tar:</i>					
			4.0 percent	95	26	6		
		8.0 percent	98	54	20			
			<i>Acetone</i>	91	0	0		
Davies and Day, 1969, Great Britain (65).	Albino mice	A. Painting shaved skin.	<i>Percent of carcinoma-bearing animals at 116 weeks</i>				The authors concluded that the lack of difference in results from the first and third groups under treatment suggests that the increased tumorigenicity of cigar tobacco is due to physical processing factors.	
		B. Varied regimen.	<i>Treatment: (actual number of animals in parentheses)</i>					
		C. Cigarette and cigar condensate.	<i>300 mg.</i>	<i>150 mg.</i>	<i>75 mg.</i>	<i>37.5 mg.</i>		
		Standard cigarette	20.1 (29)	13.2 (19)	0.7 (1)	..		
		Cigar	27.1 (39)	11.1 (16)	2.1 (3)		
	Cigar tobacco cigarette	13.9 (10)			

TABLE A14.—*Experiments concerning the effect of cigarette smoke or its constituents on tissue and organ cultures*

Author, year, country, reference	Tissue or organ culture	Material/delivery	Results
Bouchard and May, 1960, France (35).	Mouse lung.	Tobacco smoke condensate perfusion for 24 hours and subsequent grafting under renal capsule of mice.	Increased number of mitotic abnormalities in the treated cultures; particularly in the first 5-10 days after grafting.
Awa et al., 1961, Japan (16).	Human fetal lung.	Direct exposure to smoke from: a. Whole cigarettes. b. Tobacco alone. c. Paper alone.	Paper smoke induced the most severe changes, consisting of cytoplasmic vacuolization and nuclear pyknosis. Also noted were a decrease in the mitotic index and an increase in abnormal divisions, more so with paper smoke than with the other two.
Thayer and Kensler, 1964, U.S.A. (275).	KB mammalian tumor cells.	Cigarette smoke condensate application; filtered and unfiltered cigarettes.	Significant growth inhibition was shown in unfiltered smoke. Cytotoxic components were noted in both the gas and particulate phases.
Berwald and Sachs, 1965, Israel (20).	SWR mice and golden hamster embryos.	Direct application of benzo(a)pyrene [B(a)P].	Benzo(a)pyrene caused increased cell transformation as manifested by: a. Hereditary random growth pattern. b. Progressive growth as tumors after subcutaneous injection into adults. c. Ability to grow continuously in culture.
Crocker et al., 1965, U.S.A. (63).	Suckling rat trachea in organ culture.	Application of B(a)P in acetone.	Treated cultures revealed cellular metaplasia, basal cell hyperplasia, increased mitotic rate, and increased H ³ -thymidine incorporation proportional to the concentration of material and duration of application.
Diamond, 1965, U.S.A. (68).	Various continuous cell strains (mammalian).	Application of B(a)P in either dimethylsulfoxide (DMSO) or paraffin.	Inhibition of cell growth.

TABLE A14.—*Experiments concerning the effect of cigarette smoke or its constituents on tissue and organ cultures (cont.)*

Author, year, country, reference	Tissue or organ culture	Material/delivery	Results
Borenfreund et al., 1966, U.S.A. (33).	Hamster lung tissue.	Application of B(a)P in either DMSO or dimethyl- formamide.	a. Increased appearance of new small chromosomes and telocentric chromosomes. b. Increased ability to grow in hamster cheek pouch and there become spindle-cell sarcomas.
Guimard, 1966, France (110).	Chicken embryo muscular explants.	Application of tobacco extract.	Increased mitotic activity and increased incidence of anomalous mitoses.
Lasnitzki, 1968, England (160).	Mice neonatal trachea.	Application of a hydrocarbon-enriched fraction of whole smoke condensate.	a. Increased basal cell hyperplasia and pleomorphism of newly formed cells. b. Increased epithelial mitosis.
Lasnitzki, 1968, England (161).	Human fetal lung in organ culture.	Application of a hydrocarbon-enriched fraction of whole smoke condensate.	a. Cellular enlargement and promotion of growth of new bronchi. b. Increased mitoses, bronchial epithelial hyperplasia, and squamous metaplasia. c. Inhibition of stromal growth.
Chan et al., 1969, U.S.A. (54).	Mouse lung bud embryonic cultures.	Application of B(a)P in DMSO.	a. Cellular disorganization. b. Cellular pyknosis; nuclear shape and size irregularities. c. Increased epithelial mitotic rate and decreased mesenchymal mitotic rate in those cultures exposed to B(a)P versus those exposed to pyrene or DMSO.
Leuchtenberger and Leuchtenberger, 1969, Switzerland (165).	Mouse lung and kidney tissue and organ cultures.	Exposure to fresh smoke: a. Unfiltered. b. Activated charcoal filter. c. Cigarette or cigar tobacco.	a. Decreased RNA production, pyknosis, and death of cells. b. Similar results, but changes were of minimal severity. c. Similar effects as group a., but less severe.

TABLE A14.—*Experiments concerning the effect of cigarette smoke or its constituents on tissue and organ cultures (cont.)*

Author, year, country, reference	Tissue or organ culture	Material/delivery	Results
Crocker, 1970, U.S.A. (62).	Various organ cultures: a. Whole suck- ling hamster tracheas. b. Whole bron- chial tubes from late fetal dogs and monkeys.	Application of B(a)P in serum.	Squamous metaplasia; frequent pleomorphic cells; dedifferentiation of epithelium (inhibited by Vitamin A).

TABLE A15.—*Experiments concerning the effect of the instillation or implantation of cigarette smoke or its constituents into the tracheobronchial tree of animals*

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration C. Material	Results	
Blacklock, 1957, Great Britain (24).	CB white rats.	A. Injection into lung parenchyma by thoracotomy. B. Once. C. 3,4-benzpyrene in olive oil, with dead Tb bacilli or in cholesterol, cigarette "tar".	3,4-benzpyrene: a. 3 mg. in olive oil b. 3 mg. in olive oil with dead Tb bacilli c. 5.75 mg. in cholesterol pellet Cigarette "tar": a. In olive oil b. In olive oil with dead Tb bacilli Controls: a. 0.15 cc. olive oil b. 0.15 cc. olive oil with dead Tb bacilli c. Cholesterol pellets	<i>Number with tumors/number exposed</i> 5/6 sarcoma. 2/4 sarcoma, 4/8 squamous cell carcinoma. 1/8 squamous cell carcinoma. 0/10. 1/8 sarcoma, 1/8 squamous cell carcinoma. 0/4. 0/4. 0/4.
Della Porta et al., 1958, U.S.A. (67).	Syrian golden hamsters.	A. Direct tracheal instillation. B. Weekly up to 45 weeks. C. 1 percent 7,12-dimethylbenz(a)anthracene (DMBA), cigarette "tar" concentrate.	Material: a. DMBA 50 μ g./week b. "Tar" 200 μ g./week c. DMBA 50 μ g./week then "tar" 200 μ g./week d. DMBA 100 μ g./week e. DMBA 100 μ g./week and "tar" 500 μ g./week Weeks 45 32 12 30 17 20	<i>Survivors at 20 weeks/original number exposed</i> 10/20 11/21 9/20 — 7/20 9/20 <i>Number of hamsters with tracheobronchial carcinomas at death</i> 2 — — — 4 3
Rigdon, 1960, U.S.A. (221).	White Pekin ducks. Controls: 99 Experimental group: 52	A. Intratracheal injection. B. Daily for 721 days. C. Tobacco condensate in liquid petrolatum.	No neoplastic changes noted in either the experimental or control groups.	

TABLE A15.—Experiments concerning the effect of the instillation or implantation of cigarette smoke or its constituents into the tracheobronchial tree of animals (cont.)

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/or duration C. Material	Results						
Blacklock, 1961, Great Britain (25).	CB white rats.	A. Inoculation at thoracotomy.							
		B. Once and sacrificed at 1 week-2 years.	Controls	275	1.5	(1 carcinoma, 3 sarcomas).			
		C. Cigarette tobacco smoke condensate in eucerin.	Cigarette condensate	72	11.1	(6 carcinomas, 2 sarcomas).			
			Eucerin alone	44	2.3	(1 sarcoma).			
Herrold and Dunham, 1962, U.S.A. (122).	Syrian golden hamsters.	A. Intratracheal inoculation.	Material:	Number of hamsters	Number with tumors	Number of tracheo-bronchial tumors			
		B. 0.5 cc./week for 5/6 months.	B (a) in Tween60 ...	6	3	5 (3 papillomas, 2 carcinomas).			
			B (a) P in Tween60 ¹	6	3	9 (4 papillomas, 5 carcinomas).			
		C. Benzo (a) pyrene in Tween60 or olive oil.	Tween60	6	0	—			
			B (a) P in olive oil ...	6	0	—			
			Olive oil	6	0	—			
Rockey et al., 1962, U.S.A. (224).	Dogs.	A. Bronchial inoculation or stimulation.							
		B. 3-5 times/week for up to 5 years.	Procedure:	Number of dogs	Invasive carcinoma	Carcinoma-in situ	Pre-cancerous changes	Squamous metaplasia with atypical changes	Inflam-mation
		C. Cigarette smoke condensate.	Controls	27	—	—	—	6	24
			Manipulation of bronchus	25	—	—	—	7	25
			Smoke condensate	130	1	3	25	98	128
Tipton and Crocker, 1964, U.S.A. (277).	Mongrel dogs. Control group and experimental group—19.	A. Bronchial inoculation. B. Daily for 8 days. C. Cigarette smoke condensate.	Rapid induction of squamous metaplasia in condensate-exposed animals. No tabular data is presented.						

TABLE A15.—Experiments concerning the effect of the instillation or implantation of cigarette smoke or its constituents into the tracheobronchial tree of animals (cont.)

Author, year, country, reference	Animal and strain	A. Method B. Frequency and/ or duration C. Material	Results				
			Number autopsied: Male Female	Number of tumor-bearing animals	Percent tumor- bearing of survivors at 15 weeks	Total number of tumors	Total number of respiratory tract cancers
Saffiotti et al., 1966, U.S.A. (237).	Syrian golden hamsters.	A. Intratracheal inoculation. B. Weekly for 15 weeks. C. B(a)P (3 mg.) attached to fine hematite dust.	Number autopsied: Male 23 Female 17	15 11	100.0 100.0	24 17	18 16
Kuschner, 1968, U.S.A. (157).	Hamsters.	A. Wire mesh pellet implantation into bronchus. B. Lifetime. C. B(a)P, methylcholanthrene (MCA).	Implant: Wire mesh only MCA B(a)P		Number of survivors/original number in group 34/35 88/91 89/91		Number of animals with lung cancer — 43 57
Saffiotti et al., 1968, U.S.A. (235).	Syrian golden hamsters.	A. Intratracheal inoculation. B. Weekly for 15 weeks. C. B(a)P attached to a fine hematite dust.	Number autopsied: Control B(a)P in hematite Hematite only		176 55 41		Number of hamsters with respiratory tract tumors — 35 —
Borisyuk, 1969, Russia (34).	Wistar rats.	A. Intratracheal intubation. B. Monthly up to 10 months. C. Cigarette "tar".	Inoculate: Controls Unfractionated "tar" Denicotinized "tar" Neutral "tar" fraction		Number final/ initial 11/20 24/200 9/45 14/100	12 10 8 (1/9 metaplasia) 8 (2/14 carcinomas, 1/14 papillary adenoma).	Duration of inoculation (months)

¹ This group also received one injection of urethane intraperitoneally.

TABLE A16.—Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals

(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results	Comments
Lorenz et al., 1943, U.S.A. (177).	Strain A mice: †C. 97. ‡E. 97.	A. Chamber. B. Up to 693 hours. C. Cigarette smoke.	E. No increase in tumor formation over that noted in controls.	This strain of mice does have a hereditary tendency to tumor formation. †C. Control. ‡E. Experimental.
Essenberg, 1952, U.S.A. (92).	Strain A mice: C. 32. E. 36.	A. Chamber. B. 12 hours per day for 1 year. C. Cigarette smoke.	<i>Percent of lung tumors</i> C. 59.4 (19) E. 91.3 (23)	No epidermoid cancer noted; papillary adenocarcinoma was most common. Percentage difference is significant at $p < 0.01$ level.
Mühlbock, 1955, Netherlands (195).	Hybrid (020 x DBA) mice: C. 32. E. 29.	A. Chamber. B. 2 hours per day for up to 684 days. C. Cigarette smoke.	<i>Percent with alveolar carcinomas</i> C. 31.0 E. 79.0	No other type of lung tumors were found.
Leuchtenberger et al., 1958, U.S.A. (166).	CF ₁ albino mice: C. and E. 275.	A. Chamber. B. To 8 cigarettes per day from 11–201 days. C. Cigarette smoke.	<i>23 of the experimental mice showed:</i> 15 basal cell hyperplasia. 14 atypical basal cell hyperplasia. 7 dysplasia. 2 squamous cell metaplasia.	
Guerin, 1959, France (108).	IC and Wistar strain rats. C. 40. E. 100.	A. Chamber. B. 45 minutes per day from 2–6 months. C. Cigarette smoke.	<i>Percentage of rats with pulmonary tumors</i> C. 2.4 percent of 39 survivors. E. 5.1 percent of 68 survivors.	

TABLE A16.—*Experiments concerning the effect of the inhalation of cigarette smoke or its constituents upon the respiratory tract of animals (cont.)*
(Figures in parentheses represent total number survivors in specific group)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results		Comments	
Leuchtenberger et al., 1960, U.S.A. (167).	Female CF ₁ mice: C. 243. E. 360.	A. Chamber.			<i>Number with severe bronchitis; peribronchitis; atypical epithe- lial proliferation</i>	
		B. ½-6 cigarettes per day for 1 month to 2 years.	<i>Number of mice</i>	<i>Number of cigarettes</i>		<i>Exposure length (months)</i>
		C. Cigarette smoke.	151	25-1,526		1-23
			150	0		0
			36	100- 200		1- 3
			36	250- 500		4- 8
			34	600-1,600		9-23
			51	100- 400		3- 6
	63	100- 400	3- 6	17		
Leuchtenberger et al., 1960, U.S.A. (168).	Female CF ₁ mice: C. 166. E. 231.	A. Chamber.	<i>Number of mice examined</i>	<i>Exposure (days)</i>	<i>Percent of mice with pulmonary adenomatous tumors</i>	Presence of tumors showed an age- relationship independent of smoking exposure.
		B. ½-8 cigarettes per day for 17-600 days.	81	0	56	
		C. Cigarette smoke.	39	17- 99	41	
			35	100-199	37	
			51	200-600	66	
Otto, 1963, Germany (206).	Albino mice. C. 60. E. 189.	A. Chamber. B. Approximately 12 cigarettes per day for varying intervals. C. Cigarette smoke.	<i>Number of mice examined</i> E. 189	<i>Exposure</i> None. Varying up to 24 months.	<i>Number with lung tumors</i> 3 pulmonary adenomas. 21 pulmonary adenomas. 2 epithelial carcinomas.	